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ORIGINAL ARTICLE

Cardiopulmonary Bypass

A novel small animal extracorporeal circulation model for studying pathophysiology of cardiopulmonary bypass

Yutaka Fujii · Mikiyasu Shirai · Shuji Inamori · Yoshiaki Takewa · Eisuke Tatsumi

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Abstract Extracorporeal circulation (ECC) is indispensable for cardiac surgery. Despite the fact that ECCcauses damage to blood components and is non-physiologic, its pathophysiology has not been fully elucidated. This is because difficulty in clinical research and animal experiments keeps the knowledge insufficient. Therefore, it is desirable to have a miniature ECC model for small animals, which enables repetitive experiments, to study the mechanism of pathophysiological changes during ECC. We developed a miniature ECC system and applied it to the rat. We measured changes in hemodynamics, blood gases and hemoglobin (Hb) concentration, serum cytokines (TNF-α, IL-6, IL-10), biochemical markers (LDH, AST, ALT), and the wet-to-dry weight (W/D) ratio of the lung for assessing whether the rat ECC model is comparable to the human ECC. The ECC system consisted of a membranous oxygenator (polypropylene, 0.03 m^2), tubing line (polyvinyl chloride), and roller pump. Priming volume of this system is only 8 ml. Rats (400–450 g) were divided into the SHAM group ($n = 7$) and the ECC group ($n = 7$). Blood samples were collected before, 60 and 120 min after initiation of ECC. During ECC, blood pressure and Hb were maintained around 80 mmHg and 10 g/dL, respectively. The levels of the inflammatory and biochemical markers and the W/D ratio were significantly elevated in the ECC group, indicating some organ damages and systemic inflammatory responses during ECC. We successfully established the ECC for the rat. This miniature ECC model could be a useful approach for studying the mechanism of pathophysiology during ECC and basic assessment of the ECC devices.

Keywords Extracorporeal circulation · Rat ECC model · Inflammatory response · Biological reaction

Y. Fujii (✉) · Y. Takewa · E. Tatsumi
Department of Artificial Organs, National Cerebral and Cardiovascular Center Research Institute, 5-7-1, Fujishiro-dai, Suita, Osaka 565-8565, Japan
e-mail: yfujii@ncvc.go.jp

M. Shirai
Department of Cardiac Physiology, National Cerebral and Cardiovascular Center Research Institute, 5-7-1, Fujishiro-dai, Suita, Osaka 565-8565, Japan

S. Inamori
Department of Clinical Engineering Faculty of Health Sciences, Hiroshima International University, 555-36, Kurose-gakuendai, Higashi-hiroshima, Hiroshima 739-2631, Japan

Introduction

Extracorporeal life support (ECLS) devices, such as the cardiopulmonary bypass, preserve the patient's life by providing adequate oxygen supply and blood flow to vital organs [1]. However, cardiac surgery with the use of extracorporeal circulation (ECC) is often accompanied by the systemic inflammatory response, influencing significantly the morbidity and mortality after ECC [2]. Further studies are needed to elucidate the pathophysiology during ECC. However, difficulty in clinical research and animal experiments keeps its elucidation insufficient. Therefore, it is desirable to have a miniature ECC model for small animals, which enables repetitive experiments, to study the mechanism of pathophysiological changes during artificial perfusion.

In this study, we developed a miniature ECC model and applied the system to the rat. For assessing whether the rat ECC model is comparable to the human ECC, we measured changes in the hemodynamics, blood gases and Hb,

serum cytokines: tumor necrosis factor-α (TNF-α), interleukin-6 (IL-6), and interleukin-10 (IL-10), and biochemical markers: lactate dehydrogenase (LDH), aspartate aminotransferase (AST), and alanine aminotransferase (ALT), and the wet-to-dry weight (W/D) ratio of the lung.

Materials and methods

Animal

The study was approved by the National Cerebral and Cardiovascular Center Research Institute Animal Care and Use Committee, and all procedures met the National Institutes of Health guidelines for animal care.

Sprague–Dawley rats (male 400–450 g) were housed three per cage under a 12-h light–dark cycle with food and water available ad libitum.

Anesthesia, surgical preparation, and extracorporeal circulation

The animals were anesthetized with pentobarbital sodium (50 mg/kg body weight intraperitoneal injection), placed in the supine position and rectal thermocouple probe kept in place. Then, orotracheal intubation was performed using a 14G cannula (Insyte BD Medical, Sandy, Utah) and rats were ventilated with a respirator (Model SN-480-7, Shinano Seisakusho Co., Ltd, Tokyo, Japan). Ventilation was volume-controlled at a frequency of 70/min, a tidal volume of 8–10 ml/kg body weight and 100 % of inspired oxygen fraction. Rectal temperature was maintained at 36 °C throughout the experiment. Arterial blood pressure was monitored (Model 870, PowerLab system, AD Instruments, Castle Hill, Australia) via the femoral artery, which was cannulated with polyethylene tubing (SP-31 Natsume Seisakusho Co., Ltd, Tokyo, Japan). The left common carotid artery was cannulated with a polyethylene tubing (SP-55 Natsume Seisakusho Co., Ltd, Tokyo, Japan) to serve as the arterial inflow cannula for the ECC circuit. 500 IU/kg heparin sodium was administered after placement of this cannula. A 16G cannula (Insyte BD Medical, Sandy, Utah) was advanced through the right external jugular vein into the right atrium and served as a conduit for venous outflow.

The small animal ECC system (Fig. 1) consisted of a membranous oxygenator (polypropylene, 0.03 m^2: Senko Medical Co., Ltd, Osaka, Japan), tubing line (Senko Medical Co., Ltd, Osaka, Japan) and roller pump (Micro tube pump MP-3 Tokyo Rikakikai Co., Ltd, Tokyo, Japan) was primed by 5 ml of Ringer's solution, 1 ml of mannitol, 1 ml of sodium bicarbonate, and 1 ml (1000 IU) of heparin. Total priming volume of this system was 8 ml.

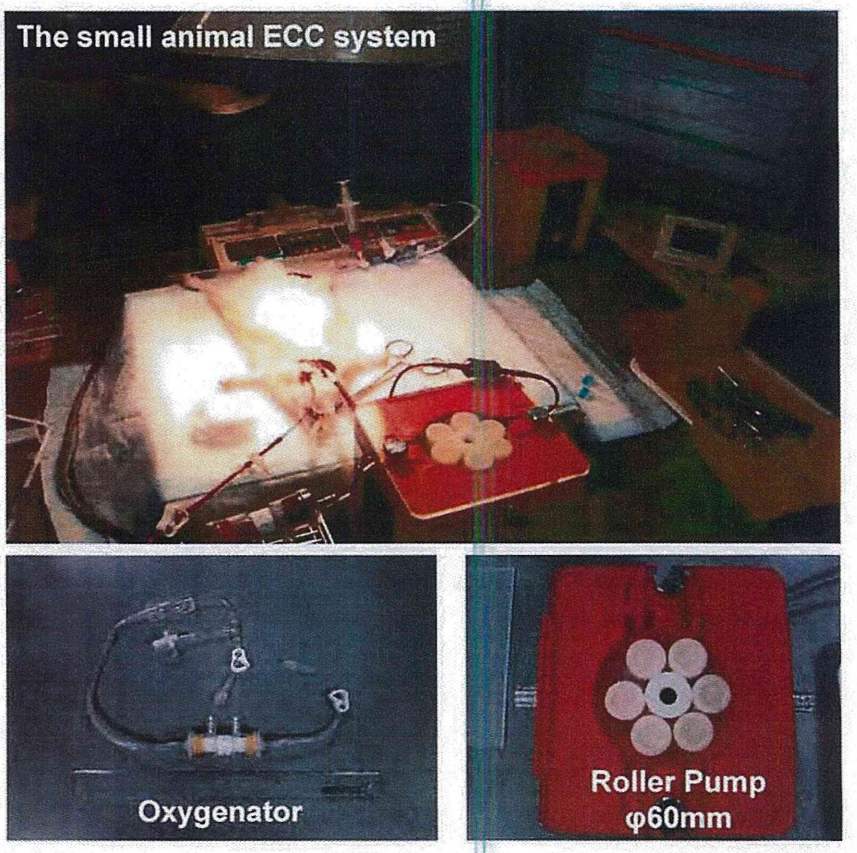

Fig. 1 The small animal ECC system. Polypropylene membranous oxygenator with membrane area of 0.03 m^2 and polyvinyl chloride tubing line (Senko Medical Co., Ltd, Osaka, Japan), and roller pump (MP-3 Tokyo Rikakikai Co., Ltd, Tokyo, Japan) are shown

Experimental design

The animals were divided into 2 groups: SHAM group ($n = 7$) and ECC group ($n = 7$). The SHAM group received surgical preparation only without CPB. In the ECC group, ECC was initiated and maintained at 70 ml/kg/min for 60 min.

Partial pressure of arterial carbon dioxide ($PaCO_2$) and partial pressure of arterial oxygen (PaO_2) were maintained at 35–45 mmHg and 300–400 mmHg. Blood samples were collected at three defined time points, before ECC (pre-ECC), 60 min after initiation of ECC. and 120 min after initiation of ECC (end-ECC).

To evaluate the inflammatory responses [3], TNF-α, IL-6, IL-10 were measured by enzyme-linked immunosorbent assay (ELISA kit, R&D systems, MN, USA). The concentrations of LDH, AST, and ALT which are used as biochemical markers for evaluating organ damage [4] were measured (DRI-CHEM 7000 Analyzer, FUJIFILM, Kanagawa, Japan).

Blood gases, pH, hemoglobin concentration, and electrolytes were also measured (ABL800 FLEX system, RADIOMETER, Copenhagen, Danmark). Animals in which the hemoglobin level declined to less than 8 g/dL at any point were excluded from the study. In general, when the hemoglobin becames 7–8 g/dL in clinical site, we consider blood transfusion [5, 6]. In this study, the purpose was to perform extracorporeal circulation without blood transfusion. All animals were killed at the end of ECC by potassium chloride injection and the left lung was harvested and divided into three parts. The superior third was used for the calculation of W/D ratio. The lung block was weighed before and after desiccation for 72 h in a dry oven at 70 °C.

Statistics

All data are expressed as mean ± standard deviation (SD). The Student's t test was used for subsequent comparison between groups at the same time points. All statistical analyses were performed using Stat-View 5.0 (Abacus Concepts, Berkeley, CA). Significance was set at $P < 0.05$.

Results

Table 1 shows the changes in hemodynamic variables, Hb concentration, PaO_2, $PaCO_2$, and level of electrolyte in the SHAM and ECC groups during experiments. During ECC, MAP and Hb were significantly decreased but were maintained around 80 mmHg and 10 g/dL, respectively. All rats' hemoglobin level did not fall below 8 g/dL at any point. There was no exclusion in the both groups. There were no significant changes in the value of the electrolyte in the both groups. However, in the ECC group, it tended to high potassium during ECC.

Table 1 Hemodynamic variables, Hb and blood gas partial pressures, and level of electrolyte before and during ECC

	Group	Pre-ECC	ECC 60 min	ECC 120 min
MAP (mmHg)	SHAM	103 ± 11	100 ± 13	105 ± 11
	ECC	102 ± 5	94 ± 24	87 ± 19*
HR (beat/min)	SHAM	387 ± 38	373 ± 38	389 ± 26
	ECC	395 ± 25	366 ± 30	365 ± 17
PaO_2 (mmHg)	SHAM	110 ± 17	106 ± 16	105 ± 14
	ECC	112 ± 12	421 ± 40*	412 ± 34*
$PaCO_2$ (mmHg)	SHAM	38 ± 3	37 ± 2	40 ± 2
	ECC	41 ± 3	40 ± 3	39 ± 3
Hb (mg/dL)	SHAM	14.7 ± 1.1	14.5 ± 0.9	14.2 ± 0.9
	ECC	15.1 ± 1.0	11.8 ± 1.1*	11.6 ± 1.0*
Na (mEq/L)	SHAM	139.6 ± 1.1	140.6 ± 1.2	141.0 ± 0.9
	ECC	138.9 ± 0.9	141.2 ± 1.0	142.0 ± 1.3
K (mEq/L)	SHAM	5.2 ± 0.2	5.4 ± 0.3	5.5 ± 0.3
	ECC	5.1 ± 0.2	5.7 ± 0.4	5.9 ± 0.5
Cl (mEq/L)	SHAM	105.6 ± 1.5	108.6 ± 1.4	107.3 ± 2.1
	ECC	106.1 ± 1.8	108.9 ± 2.2	108.7 ± 2.7

Variables are expressed by mean ± standard deviation

* $P < 0.05$ versus SHAM group at the same time

Before ECC, the serum levels of inflammatory and biochemical markers were not statistical different between the SHAM and ECC groups. Serum inflammatory and biochemical markers remained unchanged during experiment periods in the SHAM group. In the ECC group, all the systemic inflammatory markers increased significantly, reaching a maximum (TNF-α 1129 ± 137 pg/ml, IL-6 1157 ± 150 pg/ml, IL-10 385 ± 55 pg/ml) at the end of ECC (Fig. 2a–c). Additionally, in the ECC group, the levels of biochemical markers significantly increased (LDH 425 ± 65 U/L, AST 113 ± 6 U/L, ALT 55 ± 8 U/L) 60 min after the ECC initiation and increased further (LDH 708 ± 126 U/L, AST 76 ± 7 U/L, ALT 159 ± 14 U/L) 120 min after the ECC initiation (Fig. 2d–f).

The ECC group showed significantly higher W/D ratio of the lung than the SHAM group (SHAM 4.68 ± 0.18, ECC 5.46 ± 0.23) (Fig. 3).

Discussion

In this study, our small animal ECC system was able to maintain adequate levels of blood gases and Hb, and blood pressure. Furthermore, our model offers the advantage of a low priming volume not requiring transfusion in ECC group rats.

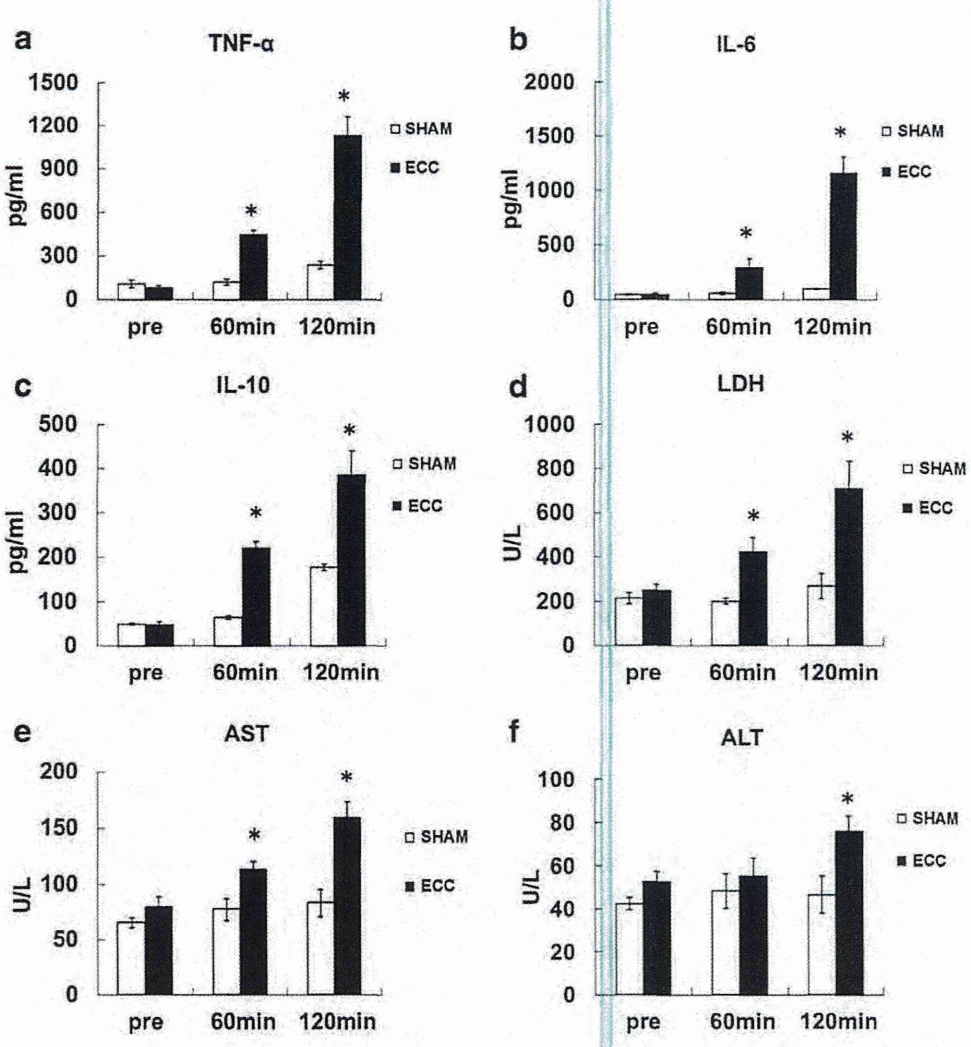

Fig. 2 Serum tumor necrosis factor (TNF)-α (**a**), interleukin (IL)-6 (**b**), interleukin (IL)-10 (**c**), lactate dehydrogenase (LDH) (**d**), aspartate aminotransferase (AST) (**e**), alanine aminotransferase (ALT) (**f**). *$P < 0.05$ versus SHAM group at the same time periods

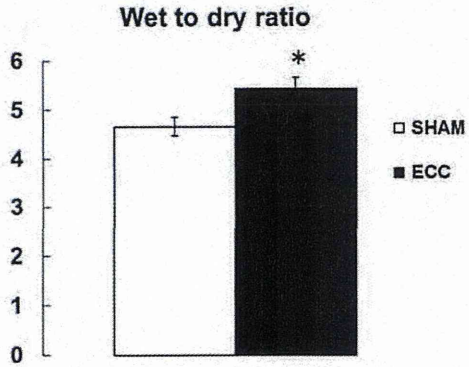

Fig. 3 Wet-to-dry ratio of the left lung at the end of CPB. *$P < 0.05$ versus SHAM group

The significant systemic inflammatory responses occurred, reaching a maximum at the end of ECC. Additionally, the biochemical markers reflecting organ damages significantly increased 60 min after the ECC initiation and increased further 120 min after the ECC initiation. The significant increase in the W/D ratio of the lung which suggests pulmonary edema [7, 8] is consistent with the previous study data [9]. From these data, our rat ECC model is considered useful for studying mechanism of pathophysiology during ECC, as an alternative to the established human ECC, which is often associated with systemic inflammation and organ damage [10].

It has been suggested that the factors responsible for the inflammatory response during ECC are blood contact with the surface of the extracorporeal circulation unit, endotoxemia, surgical trauma, ischemic reperfusion injury, and blood loss [10, 11]. Many studies showed the blood contacting surface of the ECC circuit activates white cells, platelets, and the complement system. The increase in cytokines, such as interleukins and necrosis factor [12], aggravates the inflammatory response [13]. These complex interactions during ECC lead to further inflammation [13]. In our rat ECC models, the insufflation of hydrogen which selectively reduces the hydroxyl radical could decrease the levels of serum cytokines and biochemical markers, and the

W/D ratio of the lung [7, 8]. These findings suggest that hydroxyl radical contributes toward promoting the systemic inflammatory responses and organ damages during ECC [7, 8].

In the current study, we have not been able to perform an analysis of hemolysis. The possibility of hemolysis in the ECC group cannot be denied. Therefore, in the next study, we are going to analyze for damage of blood cells. Furthermore, in the future, we will conduct research on pathophysiology of cardiopulmonary bypass by using this novel small ECC model.

Conclusion

In this study, we developed a novel small ECC model and applied the system to the rat. In our rat ECC models, we demonstrated that adequate levels of blood gases and Hb, and blood pressure were maintained and that the systemic inflammatory response and organ damages including pulmonary edema were induced associated with the production of cytokines. This novel small ECC model could be a useful approach for studying the mechanism of pathophysiology (systemic inflammation and organ damage) during ECC and basic assessment of the ECC devices.

Conflict of interest The authors have no conflict of interest directly relevant to the content of this article.

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REVIEW

Journal of Artificial Organs 2014: the year in review

Journal of Artificial Organs Editorial Committee

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Introduction

Members of the Editorial Committee of the *Journal of Artificial Organs* (JAO) are pleased to introduce to colleagues worldwide through the publication of JAO, a broad spectrum of important new achievements in the field of artificial organs, ranging from fundamental research to practical development and clinical applications. The JAO, an international journal with articles published in English, is the official journal of the Japanese Society for Artificial Organs (JSAO). We believe that JAO has a very high potential for promoting interest in the field of artificial organs not only in Japan but also in other parts of the world. We are also convinced that the specialization, originality, and level of science of this journal are at the highest in the field. The impact factor announced in the Journal Citation Reports for 2013 was 1.393. We are proud of this impact factor, which will certainly enhance international interest in the journal. Actually, the number of papers submitted to JAO has been drastically increasing during the last several years after obtaining the impact factor.

From the beginning with Volume 1 in 1998 to the last issue (Volume 17) in 2014, we have received submissions from 30 countries in the world, and we have accepted a total of 803 papers for publication through the peer-review

Y. Sawa
Division of Cardiovascular Surgery, Department of Surgery, Osaka University Graduate School of Medicine, Osaka, Japan

K. Matsuda
Emergency and Critical Care Medicine, University of Yamanashi Hospital, Yamanashi, Japan

E. Tatsumi · T. Tsukiya
Department of Artificial Organs, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan

G. Matsumiya
Department of Cardiovascular Surgery, Chiba University Graduate School of Medicine, Chiba, Japan

T. Abe
Department of Urology, Iwate Medical University School of Medicine, Iwate, Japan

K. Fukunaga
Faculty of Health Sciences, Kyorin University, Tokyo, Japan

A. Kishida
Institute of Biomaterials and Bioengineering, Tokyo Medical and Dental University, Tokyo, Japan

K. Kokubo
Department of Medical Engineering and Technology, Kitasato University School of Allied Health Science, Kanagawa, Japan

T. Masuzawa
Department of Mechanical Engineering, Ibaraki University, Ibaraki, Japan

A. Myoui
Medical Center for Translational Research, Osaka University Hospital, Osaka, Japan

M. Nishimura
Division of Organ Regeneration Surgery, Tottori University Faculty of Medicine, Tottori, Japan

T. Nishimura
Department of Therapeutic Strategy for Heart Failure, The University of Tokyo, Tokyo, Japan

T. Nishinaka
Department of Cardiovascular Surgery, Tokyo Women's Medical University, Tokyo, Japan

process. Since 2006, we have been continuing to review and summarize the articles published in JAO in the past one year to provide an overview for our readers [1–9]. We also reviewed and summarized the selected articles in volume 17 this year. In volume 17, we published 59 articles, amounting to 377 pages in total, including 34 original papers, 4 review papers, 17 case reports, 3 brief communications, and 1 technical forum. These papers were related to the many aspects of basic research, development, and clinical application of artificial organs, covering a variety of subfields. The yearly acceptance rate was 60.4 % in 2014. During the last year, a total of 95 reviewers who were specialists in artificial organs and interdisciplinary fields helped our authors to improve their manuscripts through thoughtful reviews, critiques, critiques, and suggestions. We are very happy to present such excellent work in JAO.

We would like to express our profound gratitude to all authors, reviewers, and members from all over the world and express the hope that you will continue to support our journal.

Artificial heart (basic)

Arakawa et al. [10] developed a control system for a rotary blood pump that can change rotational speed (RS) in synchrony with the cardiac cycle. The authors postulated that decreasing systolic RS using this system would alter ventricular septal movement and thus prevent RV failure. The EVAHEART ventricular assist devices were implanted into seven adult goats with inducing acute bi-ventricular dysfunction by coronary embolization. A leftward ventricular septal shift occurred in continuous and counter-pulse modes. The septal shift was corrected as a result of decreased RS during the systolic phase in counter-pulse mode.

Wu et al. [11] developed a new pressure measuring method using absolute pressure sensor without calibration. The concept of left atrial pressure (LAP) estimation using its pulsatile amplitude was proposed. The authors estimated that LAP pulsatile amplitude is affected by atrial compliance, which is changed with a magnitude of LAP. Its possibility was investigated with two long-term survived goats whose hearts were replaced with the helical flow TAHs. There existed a positive relation between mean LAP and normalized pulsatile amplitude (NPA) in manual control condition. In the 1/R control condition, relatively high correlation between mean LAP and NPA could be obtained.

Artificial heart (clinical)

Suwa et al. [12] reviewed respective role of continuous-flow implantable LVAD and paracorporeal pulsatile LVAD in current clinical practice. Because of the restriction of continuous flow pump use only for registered candidate of heart transplantation, paracorporeal pulsatile LVAD was implanted in patients in a more critical condition with lower INTERMACS profile aiming at bridge to candidacy. Some patients with pulsatile flow pump were converted to continuous-flow LVAD successfully. The overall survival was compatible in each device group. Paracorporeal pulsatile flow pumps plays an important role mainly as an option for bridge to candidacy.

Bridge to recovery using LVAD is an important strategy. Imamura et al. [13] analyzed preoperative predictors for postoperative LV reverse remodeling in patients with dilated cardiomyopathy. They demonstrated that insufficient preoperative beta-blocker therapy has significant impact on LV recovery after LVAD implantation and that patients who accomplished significant LV reverse remodeling had a better clinical course including successful weaning from LVAD support.

It is difficult to provide adequate right ventricular support in the acute phase after LVAD implantation. Inoue et al. [14] reported a severe right heart failure case who successfully treated with an extracorporeal centrifugal pump as RVAD for 5 weeks. This newly developed monopivot centrifugal pump could drive without thromboembolic event. They concluded that careful consideration is required to provide safe and effective mechanical support as a bridge-to-bridge decision or recovery of patients with severe biventricular failure.

E. Okamoto
Department of Human Science and Informatics, School of Bioscience and Engineering, Tokai University, Sapporo, Japan

S. Tokunaga
The Department of Cardiovascular Surgery, Kanagawa Cardiovascular and Respiratory Center, Yokohama, Japan

T. Tomo
Second Department of Internal Medicine, Faculty of Medicine, Oita University, Oita, Japan

Y. Yagi
Department of Clinical Engineering, Kyoto Prefectural University of Medicine, Kyoto, Japan

T. Yamaoka
Department of Biomedical Engineering, National Cerebral and Cardiovascular Center Research Institute, Osaka, Japan

Journal of Artificial Organs Editorial Committee (✉)
Osaka, Japan
e-mail: sawa@surg1.med.osaka-u.ac.jp

Nishi et al. [15] reported bridge to transplant with HeartWare LVAD, a third-generation continuous flow pump. Nine patients underwent device implantation. Except one expired case due to cerebral hemorrhage, eight patients survived without significant complication during mean of 245 days of support. HeartWare pump enabled quick implantation procedure and provided adequate support with acceptable morbidity and mortality. They suggested that HeartWare pump can be a good option for Japanese population aiming at bridge to transplantation.

The algorithm for the physiological control provided by continuous-flow LVAD has been controversial. Suzuki et al. [16] evaluated circadian variation of motor current of fixed rotation speed controlled continuous-flow LVAD. In 18 patients, a significant difference was found between the nighttime and daytime mean motor current for entire duration. The authors suspected that this maintenance of the circadian variation is based on keeping the hemodynamics stable over the long period.

Nakajima et al. [17] reported a rare case in which a large thrombus was formed in the left coronary cusp of the aortic valve after the HeartMate II LVAD implantation. The patient suddenly developed anterolateral myocardial infarction on postoperative day 16 after LVAD implantation. The patient had relatively small body size with BSA less than 1.3 m^2 and exhibited the right heart failure after LVAD surgery. The patient was rescued by emergent off-pump CABG, but stronger anticoagulation and anti-platelet regimen should have applied in such kind of patients.

Mohite et al. [18] reported that preoperative high-risk status indicated by EuroSCORE is a risk factor for poor survival in post-cardiotomy cardiogenic shock (PCCS) supported with shortterm VAD. It was also reported that CentriMag device with better durability and less complications enables longer support and better recovery of both heart and end-organ function.

Mohite et al. [19] reported a case in which it was easy to explant the Synergy micropump due to its location in subcutaneous pocket and easy access components of the device.

Yoshioka et al. [20] reported a single-center experience of Jarvik 2000 with pin bearing. Between 2005 and 2010, eight patients underwent implantation of Jarvik 2000, and the overall survival at 1, 2, and 3 years were 100, 86, and 86 %, respectively. The longest support duration was 1618 days. The Jarvik 2000 with pin bearing could support the patients with end-stage heart failure with acceptable mortality and morbidity rates.

An LVAD off test for evaluation of cardiac recovery with continuous-flow device is difficult because of intracircuit backflow from outflow graft when a device is stopped. Kashiyama et al. [21] reported an evaluation method for off test using balloon occlusion of the outflow graft. They successfully explanted implantable continuous-flow LVAD evaluating cardiac recovery exactly with off test using an occlusion balloon.

Fatullayev et al. [22] reported a case in which left ventricular reconstruction and a simultaneous LVAD implantation could be done without patchplasty making this procedure easier and decreasing the duration of the operation.

Cardiopulmonary bypass

Aoyama et al. [23] of Kitasato University studied 38 patients with acute myocardial infarction (AMI) treated with extracorporeal life support (ECLS). Fourteen patients (36.8 %) were discharged from the hospital. The outcome was not favorable for those patients with deteriorating low output syndrome (LOS) and the development of leg ischemia, hemolysis, and multiple organ failure during ECLS. In the case of patients with no complication associated with ECLS, 4.6–5.6 days after initiation of ECLS were the threshold to decide whether to switch from ECLS to VAD. Patients who suddenly developed refractory pulseless ventricular tachycardia or ventricular fibrillation without deteriorating LOS and who underwent successful PCI or CABG, and who prevented the complications associated with ECLS, showed a high probability of recovering with ECLS.

Kusajima et al. [24] of the National Cerebral and Cardiovascular Center reported a pediatric case of over 2-month ECMO. A girl patient with complicated congenital heart disease underwent fenestrated total cavopulmonary connection with extra-cardiac conduit at 3 years old. Her fenestration had spontaneously closed, and revision of fenestration was performed at the age of 5. After the operation, hypoxemia impaired the patient's cardiac function, and venoarterial ECMO with Endumo® system was conducted at 18th postoperative day. The circuit was changed three times during the first 8 days, but the fourth circuit could be used for 74 days without untoward occurrences until the patient's decease. The authors commented that a durable and safe ECMO system may provide the physicians various treatment options for the pediatric heart disease patients.

Hoashi et al. [25] of the National Cerebral and Cardiovascular Center assessed a new pediatric ECLS system (Endumo® 2000) for postoperative management after the Norwood operation. Thirty-three consecutive patients with hypoplastic left heart syndrome or its variant undergoing the Norwood operation were divided into two groups: 14 cases (7 boys 2.9 kg) with pediatric Emersave® as the ECLS devices and 19 patients (8 boys 3.1 kg) with Endumo® 2000. The demographic characteristics of both

groups showed no significant differences. Chest reentry for hemostasis during ECLS was more frequently in patients with Emersave® than with Endumo®, and the durability of Endumo® was significantly longer than that of Emersave®. The survival at discharge rate was 43 % (6/14) in Emersave® and 79 % (14/19) in Endumo®. The authors concluded that longer durability and superior antithrombogenicity of the Endumo® 2000 contributed to the improvement of outcomes after the Norwood operation.

Artificial lung/ECMO

VV-ECMO is quickly becoming a method to bridge patients with advanced pulmonary disease to lung transplantation. However, applying this method in children is carried out infrequently. Hayes et al. [26] reported the optimal use of ambulatory VV-ECMO in two adolescent patients who were successfully bridged to lung transplantation aided by tracheostomy placement.

Although prone ventilation is considered to be an effective method for improving oxygenation in patients with acute respiratory failure, in extracorporeal circulation there is a risk of cannula-related complications when changing the position. Masuda et al. [27] investigated cannula-related complications and the effect of prone ventilation on impaired oxygenation in patients who underwent ECMO. Five patients were selected as study subjects. There were no significant changes in mean arterial pressure, PEEP level, blood flow, and rotation speed of the pump when changing position. Low PaO_2/FiO_2 prior to prone ventilation was significantly increased. The authors concluded that prone positioning to improved oxygenation is a safe procedure and not a contraindication in ECMO patients.

Chen et al. [28] reported on a 65-year-old male with end-stage ischemic cardiomyopathy who underwent implantation of Levitronix VAD as a heart transplantation candidate and then developed acute pulmonary injury with profound hypoxemia. With VV-ECMO being applied, the patient was weaned from the ECMO four days later and from the ventilator on the next two days. He then underwent a successful orthotopic heart transplant after a total of 77 days on Levitronix VAD.

Sonoo et al. [29] reported a case of a successful treatment of the patient with acute respiratory distress syndrome (ARDS) after near-drowning resuscitated using ECMO more than one week. The patient was discharged without home oxygen therapy, social support, or any complication. It was probably due to sufficient lung rest for ventilator-associated lung injury during ECMO use. ICU physicians must consider ECMO even in the late phase of worsened ARDS after near-drowning.

Pacemaker

Yoshida et al. [30] investigated the electromagnetic interference (EMI) by a shoulder massage machine on implantable cardiac devices. The interference distance between the massage machine and the implantable cardiac pacemaker was within 28 cm, and they reported possibility of erroneous ventricular fibrillation on the ICD patient by the massage machine. From the result, they suggested necessary of warning on the massage machine and necessary of caution to the patient. Yoshida et al. [30] investigated the electromagnetic interference (EMI) by a shoulder massage machine on implantable cardiac devices. The interference distance between the massage machine and the implantable cardiac pacemaker was within 28 cm, and they reported possibility of erroneous ventricular fibrillation on the ICD patient by the massage machine. From the result, they suggested necessary of warning on the massage machine and necessary of caution to the patient.

Taguchi et al. [31] reported a case of a patient who developed recurrent contact dermatitis after 16 years of pacemaker implantation. The patient did not show any sensitivity to titanium, but she demonstrated sensitivity to silicone. Thus, they covered not only the generator but also the lead with polytetrafluoroethylene (PTFE). The result was that the patient suffered no further episodes of pacemaker-associated contact dermatitis.

Artificial valve

Ushijima et al. [32] analyzed the left ventricular (LV) performance after AVR with the 16-mm ATS mechanical valve, based on the concept of cardiac energetics analysis with echocardiographic examination (Ees, Ea, Ea/Ees, and SW/PVA). They showed that the midterm LV performance after AVR with the 16-mm ATS mechanical valve was satisfactory.

Teshima et al. [33] compared the midterm outcomes after aortic valve replacement (AVR) between 17-mm SJM mechanical heart valves (MV) and 19-mm bioprosthetic valves (BV) in elderly patients with small aortic annuli in elderly patient. They demonstrated that AVR using 17-mm MV in elder patients with small aortic annuli provided equivalent midterm clinical results to that with 19-mm BV.

Biomaterials

Sato et al. [34] reported a novel crosslinking reagent, triglycidylamine (TGA), for treating bioprosthetic valve or pericardium. TGA crosslinked the tissue very slowly and

suppressed the calcification well. The calcium deposition mechanism for TGA-crosslinked and glutaraldehyde-crosslinked tissue seems to be different.

Ehashi et al. [35] reported the tissue reaction (M1/M2 macrophage recruitment and IL-1b, IL-6, IL-10, TGFb expression) to different biodegradable materials. PLA-PEG multiblock copolymer showed high degradability and very mild tissue reaction as well as the acellular collagenous tissue.

Tissue engineering/regenerative medicine

Mizutani et al. [36] of Mie University studied ligament cells from the anterior cruciate ligament (ACL) and periodontal ligament (PDL) for preparing tissue-engineered artificial ligaments. Firstly, they prepared highly oriented extracellular matrix (ECM) using elastin-A and collagen. Using the cells and matrices, they reported that elastin-A promotes the osteogenic differentiation of ligament cells and that collagen maintains the phenotype of ligament cells.

Sakakibara et al. [37] reported the evaluation of blood vessel reconstruction process of decellularized small-diameter vessels prepared by a hyperosmotic electrolyte solution treatment. All acellular vessels transplanted into the rat abdominal aorta were patent up to 14 months. They found that the acellular vessels prepared with hyperosmotic electrolytic solution showed excellent and long-term patency, which may be related to the successful preservation of vascular ECM, and that the acellular vessels revealed the intima/medulla regeneration with the physiological contraction–relaxation functions in response to the each substance.

Artificial kidney/dialysis

PD-related peritoneal injury factors induced by bioincompatible PD fluid accumulated in the peritoneum and might induce EPS. Nakamoto et al. [38] reported the accumulation of advanced glycation end products (AGE) and beta2-microglobulin (b2M) in peritoneum in long-term PD patients. They concluded that the increased proportion of AGE and b2M deposition induced by long-term exposure of PD fluid may be a marker of peritoneal injury.

Nishimura et al. [39] reported a case of severe ifosfamide intoxication successfully treated using blood purification therapy. Since the incorporation of ifosfamide into treatment protocols, osteosarcoma has dramatically improved. However, ifosfamide may be limited by serious side effects: so-called ifosfamide intoxication. They suggested the efficacy of blood purification therapy for the treatment of severe ifosfamide intoxication and the effects of blood purification therapy on ifosfamide pharmacokinetics.

Narayan et al. [40] reported a case treated with 5 % albumin continuous venovenous hemodialysis in a 31-year-old female who developed CNS depression, hypotension, and respiratory failure, requiring mechanical ventilation, after an intentional ingestion of approximately 10 g of extended release carbamazepine. The peak drug level was 26 mcg/ml (with toxicity often developing a level above 15 mcg/ml). The drug level was dramatically reduced to normal range; she recovered fully on day 3 without significant neurologic sequelae.

Artificial liver, pancreas

Liu et al. [41] compared outcomes of conventional islet culture at 37 °C in RPMI-1640 medium, cold preservation at 4 °C in University of Wisconsin (UW) solution, and cryopreservation at −80 °C with dimethyl sulfoxide to determine the optimal method for islet preservation, which is crucial to achieve successful and efficient islet transplantation. After short-term (1 day) or long-term (7 days) preservation, cold preservation at 4 °C showed higher recovery rate of the islet number, lower percentage of dead cells to viable cells, and better insulin release ability in comparison with the islet culture at 37 °C or cryopreservation at −80 °C, suggesting that cold preservation at 4 °C in UW solution is the optimal method in comparison with the conventional culture or cryopreservation for short-term and long-term islet preservation.

Artificial skin, muscle, bone/joint, neuron

Porous calcium phosphate ceramic granules are popular bone-substituting materials for the treatment of bone void. Choi et al. [42] reported better healing process of bone defects by Tetrabone®, a newly developed granular artificial bone of unique four-legged shape compared to standard irregular-shape ceramic granules in a rabbit model. Tetrabone® nicely supported new bone formation, while its resorption progressed slowly.

Modular head/neck/stem system combining ceramic or metal head with metal neck/stem is currently popular in hip arthroplasty. Carbon fiber-reinforced polyetheretherketone (CFR-PEEK) is an attractive biomaterial for hip prosthesis with excellent mechanical properties and low risk of adverse biological reaction compared with metal. Nakahara et al. [43] reported superior fixation strength of taper connection between CFR-PEEK neck and ceramic head over titanium alloy/ceramic combination.